Miniaturized iPS-Cell-Derived Cardiac Muscles for Physiologically Relevant Drug Response Analyses.

Journal: Sci Rep

Publication Year: 2016

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PubMed link: 27095412

Funding Grants: Gladstone CIRM Scholars Program

Public Summary:
Tissue engineering approaches have the potential to increase the physiologic relevance of human iPS-derived cells, such as cardiomyocytes (iPS-CM). However, forming Engineered Heart Muscle (EHM) typically requires >1 million cells per tissue. Existing miniaturization strategies involve complex approaches not amenable to mass production, limiting the ability to use EHM for iPS-based disease modeling and drug screening. Micro-scale cardiospheres are easily produced, but do not facilitate assembly of elongated muscle or direct force measurements. Here we describe an approach that combines features of EHM and cardiospheres: Micro-Heart Muscle (μHM) arrays, in which elongated muscle fibers are formed in an easily fabricated template, with as few as 2,000 iPS-CM per individual tissue. Within μHM, iPS-CM exhibit uniaxial contractility and alignment, robust sarcomere assembly, and reduced variability and hypersensitivity in drug responsiveness, compared to monolayers with the same cellular composition. μHM mounted onto standard force measurement apparatus exhibited a robust Frank-Starling response to external stretch, and a dose-dependent inotropic response to the β-adrenergic agonist isoproterenol. Based on the ease of fabrication, the potential for mass production and the small number of cells required to form μHM, this system provides a potentially powerful tool to study cardiomyocyte maturation, disease and cardiotoxicology in vitro.

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